



HAL
open science

Host proteins involved in HIV infection: New therapeutic targets

Nathalie Arhel, Frank Kirchhoff

► To cite this version:

Nathalie Arhel, Frank Kirchhoff. Host proteins involved in HIV infection: New therapeutic targets. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 2010, 1802 (3), pp.313. 10.1016/j.bbadis.2009.12.003 . hal-00560300

HAL Id: hal-00560300

<https://hal.science/hal-00560300>

Submitted on 28 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Manuscript

Host proteins involved in HIV infection: New therapeutic targets

Nathalie Arhel, Frank Kirchhoff

PII: S0925-4439(09)00296-8
DOI: doi:[10.1016/j.bbadis.2009.12.003](https://doi.org/10.1016/j.bbadis.2009.12.003)
Reference: BBADIS 63042

To appear in: *BBA - Molecular Basis of Disease*

Received date: 26 October 2009
Revised date: 8 December 2009
Accepted date: 8 December 2009



Please cite this article as: Nathalie Arhel, Frank Kirchhoff, Host proteins involved in HIV infection: New therapeutic targets, *BBA - Molecular Basis of Disease* (2009), doi:[10.1016/j.bbadis.2009.12.003](https://doi.org/10.1016/j.bbadis.2009.12.003)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 Host proteins involved in HIV infection: New therapeutic targets

2 Nathalie Arhel, Frank Kirchhoff*

3

4 Institute of Molecular Virology

5 Universitätsklinikum Ulm

6 Albert-Einstein-Allee 11

7 781089 Ulm

8 Germany

9

10

11 *Address correspondence to:

12

13 Nathalie Arhel

14 Phone: 33-1-40613599

15 Fax: 33-1-40613465

16 nathalie.arhel@pasteur.fr

17

18 or

19

20 Frank Kirchhoff

21 Phone: 49-731-50065109

22 Fax: 49-731-50065131

23 frank.kirchhoff@uniklinik-ulm.de

24

25

26

27ABSTRACT

28Current treatment of HIV/AIDS consists of a combination of three to five agents targeting
29different viral proteins, i.e. the Reverse Transcriptase, Protease, Integrase and Envelope,
30and aims to suppress viral replication below detectable levels. This “highly active
31antiretroviral therapy” (HAART) has brought an enormous benefit for life expectancy and
32quality in HIV-1-infected individuals, at least in industrialized countries. However, significant
33limitations with regard to efficiency, drug-resistance, side-effect and costs still exist. Recent
34data suggest that cellular factors also represent useful targets for therapy. Here, we
35summarize findings from several genome-wide screens that identified a large number of
36cellular factors exploited by HIV-1 at each step of its life cycle. Furthermore, we discuss the
37evidence that humans are equipped with powerful intrinsic defense mechanisms against
38retroviruses but that HIV-1 has evolved elaborate ways to counteract or evade them.
39Preventing the use of host-cell proteins obligatory for viral replication or strengthening the
40cellular defense mechanisms may help to reduce viral replication to harmless levels. A better
41understanding of the host factors that promote or restrict HIV-1 replication may thus lead to
42the development of novel therapeutics against HIV/AIDS.

431. Introduction

44 Currently, more than 25 antiretroviral drugs are available to treat human
45immunodeficiency virus (HIV) infection. The great majority of them target the HIV-1 reverse
46transcriptase (RT) (nucleoside and nucleotide RT inhibitors: zidovudine, didanosine,
47zalcitabine, stavudine, lamivudine, abacavir, emtricitabine and tenofovir and non-nucleoside
48RT inhibitors: nevirapine, delavirdine, efavirenz and etravirine) and the viral protease
49(saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, fosamprenavir,
50tipranavir and darunavir) (Fig. 1). More recently, antiretroviral drugs that inhibit the viral
51integrase (IN) (raltegravir) or the six-helix bundle core formation of the gp41 transmembrane
52protein required for virus-cell fusion (enfuvirtide), have been approved for the clinic [1]. While
53this growing repertoire of antiretroviral agents is impressive, none of these drugs is useful for
54the treatment of HIV/Acquired Immunodeficiency Syndrome (AIDS) on its own because HIV-
551 is highly variable and capable of developing resistance against all of them. This high
56genetic variability provided the rationale for the development of “highly active antiretroviral
57therapy” (HAART) consisting of combinations of three or more antiretroviral agents. HAART
58aims to suppress viral replication to such low levels that the emergence of drug-resistant
59HIV-1 variants is prevented. Furthermore, while the diverse HIV-1 species (called quasi-
60species) found in a single individual will most likely already contain the genetic changes
61reducing its susceptibility to single drugs, it is more difficult for the virus (and sometimes
62associated with decreased “fitness”) to acquire the complex combination of mutations
63required for multi-drug resistance.

64 Treatment of HIV-1-infected individuals by HAART usually allows to reduce the plasma
65viral load to undetectable levels, improves CD4+ T cell counts, delays disease progression
66and promotes survival. However, although the development of HAART was certainly the
67greatest success of AIDS research and allows the reduction of morbidity and mortality
68wherever it is available, it also has major limitations. Furthermore, HAART is expensive and
69requires an infrastructure with a functional health care system allowing the medical
70monitoring of the success of antiretroviral therapy to prevent or at least delay the emergence
71of drug-resistant HIV-1 strains. The vast majority of the ~34 million people currently infected
72with HIV-1 live in developing countries and – although access to antiretroviral drugs in the
73developing world is improving – most of them still do not have access to antiretroviral therapy
74[2, 3]. Thus, while HAART constitutes an effective approach for the treatment of AIDS and
75also prevents HIV-1 transmission by reducing the viral loads, it still has little impact on the
76global spread of the virus (~2.5 million new HIV infections per year) and the global number of
77fatalities caused by AIDS (~2 million per year). Life expectancy has drastically fallen in some

78countries that are most severely affected by HIV/AIDS, e.g. in Zimbabwe it is only 34 years
79for women and 37 years for men [2]. Even under optimal conditions, HAART has significant
80drawbacks, e.g. it is frequently associated with significant side effects (such as metabolic and
81cardiovascular disorders), with immune reconstitution disease, and with the development of
82resistant HIV-1 strains (particularly in the case of patients' non-adherence to treatment).
83Furthermore, HAART requires life-long daily treatment because it does not allow integrated
84proviruses to be eliminated from resting long-lived cells and thus fails to eradicate the virus
85entirely.

86 Because of the drawbacks of current combination antiretroviral therapy it remains a
87major interest to develop new antiretroviral drugs or innovative therapies to reduce undesired
88side-effects, to prevent the emergence of drug resistance or even to attack the viral
89reservoirs [4,5]. Indeed, a major barrier to curing HIV infection remains the ability of HIV to
90integrate in the host genome and remain latent. The thus-generated viral reservoirs cause
91viral rebound upon HAART interruption and impose life-long antiretroviral therapy with its
92many associated side-effects and possible development of resistance. Here, we focus on
93approaches aiming to target cellular rather than viral proteins. It is long known that HIV-1
94utilizes host factors at many steps of its life cycle. However, currently only a single drug
95targeting a cellular protein has been approved for the clinic: Maraviroc binds to the HIV-1
96entry cofactor CCR5 and blocks its interaction with the viral envelope gp120 to prevent the
97membrane fusion events necessary for viral entry [6]. Recent studies using genome-wide
98screening technologies have identified large numbers of host factors that may be required for
99virus replication and thus represent potential therapeutic targets [7-9]. Another recent
100development is the realization that humans are equipped with factors that directly inhibit
101retroviruses [10, 11]. For example, tripartite motif 5-alpha (TRIM5 α) proteins can block
102incoming retroviral capsids in a species-specific manner [12] and the cellular apolipoprotein
103B mRNA-editing enzyme, catalytic polypeptide-like 3 (APOBEC3) cytidine deaminase
104induces lethal hypermutation of the viral genome [13]. Finally, the recently discovered
105restriction factor "tetherin" (also called BST-2, HM1.24 or CD317) inhibits HIV-1 particle
106release [14, 15]. These ancient antiviral defense mechanisms were obviously quite
107successful in past encounters with retroviruses, since about 8% of the human genome is of
108retroviral origin [16]. HIV-1, however, has evolved the ability to counteract these by several
109"accessory" viral proteins (Viral infectivity factor (Vif), viral protein U (Vpu)) or can avoid them
110by its high variability and is thus capable to replicate efficiently in the hostile environment of
111the human cell [10, 11]. Strengthening these cellular defense mechanisms or weakening the
112viral antagonists may help to control HIV-1 replication.

113

1142. Host factors as targets for antiretroviral therapy

1152.1 Targeting viral entry

116 All viruses are obligate intracellular parasites without an independent metabolism and
117 thus strictly dependent on their target cells for reproduction. The first cellular factor shown to
118 be required for HIV-1 replication is the primary viral CD4 receptor that has been discovered
119 more than two decades ago and determines the viral tropism for CD4⁺ T cells and tissue
120 macrophages [17]. A variety of strategies has been pursued to block the interaction between
121 the external viral envelope glycoprotein gp120 and CD4. These include soluble CD4 or CD4
122 mimics that seem to induce a non-functional conformation of gp120, small molecule inhibitors
123 that target the conserved CD4-gp120 binding site, as well as CD4 antibodies [18]. One CD4
124 antibody (TNX-355) has shown some beneficial effects in clinical studies [19] and seems to
125 act synergistically with enfuvirtide (T20) that interacts with gp41 and blocks a later step in the
126 viral entry process [20]. However, TNX-355 has the disadvantage that it is not orally
127 bioavailable and currently no CD4 inhibitor has been approved for the clinic.

128 Ten years after the discovery of CD4 as primary receptor of HIV, the seven-
129 transmembrane G protein-coupled chemokine receptors CCR5 and CXCR4, were
130 discovered as critical coreceptors for HIV-1 entry [21-25]. Shortly thereafter, several groups
131 reported that a homozygous deletion in the *CCR5* allele ($\Delta 32/\Delta 32$), naturally occurring in
132 about 1% of the Caucasian population, protects against HIV-1 infection and is not associated
133 with significant immunological dysfunction [26-28]. Moreover, it was observed that
134 heterozygous deletions in *CCR5* are associated with delayed disease progression [27-29].
135 Altogether, these results suggested that CCR5 is a promising cellular target for anti-HIV
136 therapy because its blockade should be well-tolerated and effective in inhibiting CCR5-tropic
137 (R5) HIV-1 strains. Initially, several modified forms of the natural CCL5/RANTES (Regulated
138 upon Activation, Normal T cell Expressed and Secreted) ligand of CCR5 have been
139 developed [30]. These agents compete with the HIV-1 gp120 for CCR5 binding and some of
140 them (e.g. PSC-RANTES) are highly effective *in vitro* and in the human peripheral blood
141 lymphocyte-Severe Combined Immunodeficient (SCID) mouse model [30, 31]. Although they
142 failed in clinical trials, PSC-RANTES is currently further evaluated as potential microbicide
143 against HIV [32, 33]. Another strategy was the development of small molecule inhibitors that
144 bind to a hydrophobic pocket in CCR5 and seem to inhibit HIV infection by inducing
145 conformational changes rather than by direct occupation of the gp120 binding site [18]. One
146 of these inhibitors, Maraviroc, has been approved by the US Food and Drug Administration
147 (FDA) and the European Medicine Agency for the treatment of viremic patients harboring
148 multi-resistant HIV-1 strains. Thus, maraviroc is currently the only antiretroviral drug targeting
149 a cellular factor used in the clinic [34]. However, several related agents, such as vicriviroc,

150and anti-CCR5 antibodies are currently evaluated in clinical trials [35, 36].

151 An alternative approach is the specific knock-down of *CCR5* using RNA interference.
152Although this method usually only achieves partial knock-down of the target sequence, one
153study achieved the complete knock-out of *CCR5* in hematopoietic stem cells using a stable
154RNA interference system, which then conferred resistance to HIV-1 infection to the *in vitro*
155derived macrophages [37]. More recently, the specific delivery of *CCR5* siRNAs to T cells in
156a humanized mouse model was reported to suppress viremia and prevent CD4 T-cell
157depletion [38]. Work is underway to reduce induced cytotoxicities to adapt siRNA-mediated
158knock-down of *CCR5* for clinical application. These strategies have recently obtained
159substantial impetus by the spectacular report of a $\Delta 32/\Delta 32$ allogenic stem cell transplantation
160in an HIV-1 positive leukemia patient, which led to long-term control of viral replication (for
161more than 2 years) in the absence of antiretroviral therapy [39]. Since HIV-1 usually only
162requires a few amino acid changes to switch from *CCR5* to *CXCR4* coreceptor usage [40],
163this is a highly unexpected and encouraging finding. The transplantation of *CCR5*-negative
164allogenic stem cells for the treatment of malignancies in HIV-1 positive patients holds some
165promise, particularly if the worldwide bone marrow and cord blood donor banks agree to
166merge *CCR5*-screening information into one database system [41]. A more general approach
167would be to knock-down *CCR5* in wild-type CD34+ stem cells using RNA interference before
168transplantation. In order to be successful, this approach would have to allow the specific
169expansion of the transgenic cells *in vivo* since it is unlikely that gene transfer (of an siRNA
170expressing cassette) is achieved in all cells of the transplant. However, HIV-1 may facilitate
171this selection by causing a specific depletion of *CCR5*-expressing cells.

172 Although the inhibition or knock-down of *CCR5* using small inhibitor molecules or gene
173therapy transfer protocols is promising, it also has some drawbacks. One concern is that
174*CCR5* may play a role in immunity against some pathogens [42]. Another disadvantage is
175that it is not active against X4 HIV-1 strains. Obviously, the best approach would be to
176combine *CCR5* and *CXCR4* inhibitors [43]. However, in contrast to *CCR5*, *CXCR4* is
177essential for various physiological processes and its knock-out is lethal in mice [44, 45].
178Several potent inhibitors of *CXCR4*, such as AMD3100 or AMD070, have been developed
179but clinical development was halted due to undesired side effects or lack of antiviral effects
180[1, 18]. Notably, however, AMD3100 has been approved by the FDA as a stem cell mobilizer
181for transplantation under different names (Plerixafor or Mozobil). Several new anti-*CXCR4*
182agents are in development and the *CXCR4*/*SDF-1* pathway is emerging as an appealing
183target for the treatment of certain forms of cancer [46]. Thus, potent and better-tolerated
184*CXCR4* inhibitors may become available in the future and complement antiretroviral
185therapies targeting *CCR5*.

186

1872.2 Other cellular targets for antiretroviral therapy currently investigated

188 HIV-1 entry is a particularly promising step for intervention because it involves several
189relatively well-defined interactions in the cell membrane that can be blocked without the
190inhibitor entering the cells [47]. Furthermore, blocking HIV-1 at this early step prevents the
191integration of the proviral genome into that of the host cell and hence the establishment of
192latent viral reservoirs. However, the HIV-1 replication can in theory be inhibited at each step
193of its cycle in order to block viral spread. Thus, the inhibition of HIV-1 uncoating, reverse
194transcription, integration, transcription, assembly and release from the cell membrane (Fig. 1)
195all represent valid approaches to tackle HIV-1 infection and are currently being investigated.

196 An early therapeutic approach sought to target the HIV co-factors Tat and Rev, which are
197essential for viral replication and, to a large extent, functionally dependent on well-defined
198cellular factors [48]. Tat promotes the elongation of viral transcripts by binding to the
199transactivation response element (TAR) located in the HIV long-terminal repeat (LTR) and
200acts as an adaptor for the recruitment of the positive transcription elongation factor b (P-
201TEFb) [49], which is a heterodimer of cyclin T1 and cyclin dependent kinase 9 (Cdk9). Since
202recruitment of P-TEFb to the TAR is both necessary and sufficient for HIV-1 transcription
203[50], targeting P-TEFb may constitute a good approach for anti-HIV therapy. A number of
204small compounds that inhibit Cdk9 or cyclin T1 activities, or that disrupt the Tat/TAR/P-TEFb
205interaction have been tested [51, 52]. However, since P-TEFb is necessary for the
206transcription of many cellular genes [53], finding an inhibitor that exclusively blocks HIV
207transcription has proven difficult. Rev mediates the nuclear export of unspliced viral RNA
208through interaction with the cis-acting Rev response element (RRE) located in the HIV *env*
209gene [54, 55]. The shuttling of Rev between the nucleus and the cytoplasm is dependent on
210a number of cellular proteins, including the RNA helicase DDX3X, CRM1, Ran-GTP, as well
211as nucleoporins, importins and Sam 68 [54-56]. Targeting of DDX3X or other DEAD-box
212helicases by RNA interference has been reported to suppress Rev function and inhibit HIV
213replication [57-59]. Interestingly, the Tat co-factor CCNT1/cyclin T1 and the Rev co-factor
214DDX3X were identified in two of the three siRNA screens of host factors implicated in HIV-1
215infection [7-9]. However, although Tat and Rev represent useful targets for antiretroviral drug
216development, no specific agents inhibiting them or their cellular cofactors without significant
217side effects have yet been developed.

218 The recent addition of an HIV-1 IN inhibitor (raltegravir) to the available HAART drugs
219indicates that targeting proviral integration is a useful approach. HIV-1 IN interacts with a
220cellular factor that may have potential as a therapeutic target: the cellular lens epithelium-
221derived growth factor (LEDGF)/p75 [60], a chromatin-associated protein that is important for

222HIV-1 integration [61]. Disruption of the interaction between HIV-1 IN and LEDGF/p75 leads
223to impaired viral replication [62]. The crystal structure of the interaction interface has been
224resolved [63, 64] and the development of a small inhibitor to preclude LEDGF/p75–IN binding
225is conceivable but remains challenging [65].

226 Although post-integration, the inhibition of particle budding from the plasma membrane
227and/or cell-to-cell transfer of the virus is a valid approach to prevent viral spread. HIV-1
228usurps the cellular Endosomal Sorting Complex Required for Transport I (ESCRT-I) for its
229release from infected cells [66-68]. In particular, the PTAP-type late domain of the HIV-1 Gag
230precursor polyprotein interacts with TSG101 (tumor susceptibility gene 101), a cellular
231protein normally involved in endosomal protein sorting, and inhibition of this interaction or
232depletion of TSG101 by RNA interference suppresses HIV-1 particle release [69-71]. One
233therapeutic approach would consist in developing molecules, which would mimic the viral
234PTAP motif, such as cyclic peptides [72]. Another potentially interesting interaction has also
235been identified between HIV-1 Gag and the endosomal sorting protein Alix [73, 74].

236

237**2.3 Genome wide screens reveal numerous potential targets for antiretroviral therapy**

238 Although many cellular factors were already known to be required for HIV infection, the
239recent application of technological advances to the study of HIV infection revealed that we
240were actually only seeing the tip of the iceberg. Three independent genome-wide RNA
241interference-based screens evaluated more than 20,000 human genes for their relevance in
242infection [7-9]. Altogether, these studies identified a total of 842 genes that reduce HIV-1
243infection when knocked-down. Another study used an alternative approach and genotyped a
244large group of HIV-1-infected individuals to identify human genetic differences that influence
245the vulnerability to HIV-1 infection and clinical outcome of infection [75], thus adding a further
24663 genes to the list. Recently, the National Library of Medicine made available a
247comprehensive list of all cellular proteins shown to interact physically or functionally with HIV-
2481 (HIV-1, Human Protein Interaction Database) [76-78]. Taken together, these studies and
249databases identified a total of 1,254 genes that may play a role in HIV-1 replication [79].
250Many of these genes are involved in specific pathways (proteasomal targeting, transcription,
251immune response, RNA binding/splicing, chaperones etc.) that are usurped by HIV-1
252(summarized in Table 1).

253 The whole-genome siRNA screens, which expand the information brought by a previous
254subgenomic screen [80], provide important new insights on the host factors involved in HIV-1
255early steps of replication. However, some caution must be taken in interpreting this newly
256available source of information. Firstly, the siRNA screens show only poor overlap: only three

257of the 842 HIV-dependency factors were obtained in all three studies: MED6, MED7 and
258RELA. The reason for this poor overlap lies possibly in differences in the cell lines used
259(HeLa and HEK293T), the multiplicity of siRNA coverage for each gene, the steps of the HIV
260replication cycle investigated, the time points analyzed, and the filtering thresholds used [79].
261Secondly, the use of cell lines (i.e. HeLa and HEK293T) that are not usually infected by HIV-
2621 and of pseudotyped virions limits the relevance of some of these results. Recently
263however, a genome-wide siRNA-based screen was carried out in Jurkats, thus identifying a
264further 252 genes involved in HIV-1 infection, only 6 of which were also identified by the 3
265siRNA screens carried out in HeLa and HEK293T [81]. Thirdly, the siRNA screens focus per
266definition on proteins whose functions may be knocked-down without overt cytopathic effect,
267in other words for proteins that are either functionally redundant or that are not essential for
268cellular function. Fourthly, it is likely that many hits represent false positives in terms of
269physiological relevance since the studies only look at virus infection in cell lines as
270experimental end-point and it is by no means certain that these play significant roles in HIV-1
271infected individuals. These points, together with the partial knockdown nature of RNA
272interference, probably account for the fact that some cellular factors already known to be
273important for HIV-1 infection were missed by the genome-wide surveys (e.g LEDGF/p75).

274 Despite some limitations, the genome-wide screens and surveys of HIV infection provide
275a good starting point for the identification of cellular targets for HIV therapy. Cellular factors
276that were identified in at least two of the three siRNA screens and are listed in the HIV
277interaction database represent particularly interesting candidates. Eleven proteins fulfill this
278criterion: the nucleoporin Nup153, CD4 and CXCR4, the kinases Jak1 and Akt1, the NFkB
279subunit RelA, four co-factors for HIV-1 accessory and regulatory proteins, and a keratan
280sulfotransferase of HIV-1 envelope [79]. Other interesting candidates are those appearing in
281three or more gene sets from a total of twelve that are currently available for factors identified
282as relevant for HIV replication [79]. In this case, 49 genes fulfill this criterion including Nup98,
283Nup153 and hnRNP1, all of which are thought to play a role in HIV nuclear import, as well as
284TSG101 involved in virion assembly [79]. Proteasomal and lysosomal subunits, chaperones,
285heat shock proteins and transcription/translation factors also constitute multiple hits, but
286whether these are sufficiently important for HIV replication as to constitute a good drug target
287and can be selectively inhibited without cellular toxicity remains to be determined. These
288future studies and further improved RNAi-based screens have the potential to identify
289essentially all cellular cofactors required in the different steps of the HIV-1 life cycle and will
290undoubtedly not only greatly improve our understanding of host/HIV interactions but also
291lead to the development of new antiretroviral agents.

292

2933. Host factors restricting HIV-1 replication

294 It is well appreciated that HIV uses many cellular factors to complete its life cycle. Only in
295 recent years, however, has it become clear that the host cell is not a friendly environment for
296 HIV since several host proteins have been identified as intrinsic immunity factors that most
297 likely evolved specifically as defense against viral infections [10, 11]. These host restriction
298 factors interfere with retroviral replication by diverse mechanisms and can protect mammals
299 from cross-species transmission of retroviruses. Three classes of retroviral restriction factors
300 have so far been identified: cytidine deaminases (e.g APOBEC3G), which induce lethal
301 hypermutations of the retroviral genome [82, 83], Fv1/TRIM5 α proteins, which restrict the
302 incoming retroviral capsid [84, 85] and tetherin, which impedes the release of nascent HIV
303 virions from the cell surface [14]. Recent analyses have shown that these host restriction
304 factors all evolved under positive selective pressure due to past encounters with ancient
305 viruses [86-89]. Overall, they were obviously quite successful, since a large part of our
306 genome (about 8%) consists of silenced retroviral sequences [16] and are still active against
307 endogenous and exogenous invaders [90, 91]. Notably, most restriction factors have broad
308 antiviral activity and strengthening them may have beneficial effects against different
309 pathogens [10, 11, 91].

310 APOBEC3G was the first host gene identified as an inhibitor of HIV-1 infection [13].
311 APOBEC3G is a cytidine deaminase that introduces G-to-A substitutions in the HIV-1
312 genome, which are detrimental to viral replication (Fig. 2). It has been reported that high
313 levels of hypermutation in the provirus are associated with higher CD4 T cell counts in
314 infected individuals [92], although not with reduced viral loads [93, 94]. Accumulating
315 evidence suggests that some of the antiretroviral activity of APOBEC3 is independent of its
316 mutator activity and may involve direct effects on reverse transcription or integration [11]. An
317 increasing interest is attributed to the therapeutic inhibition of Vif, which antagonizes
318 APOBEC3G by proteasome-mediated degradation and blocking its incorporation into
319 nascent particles [95, 96]. A different approach would be to boost the intracellular levels of
320 APOBEC proteins through interferon-alpha treatment [97, 98], or by targeting the Vif-
321 APOBEC interaction domain. Alternatively, small molecules may be designed to enhance the
322 catalytic activity of APOBEC3G in the cell. However, in order to consider APOBEC family
323 members as potential targets for anti-HIV therapy, it will be important to clarify the relative
324 contribution of the enzymatic and non-enzymatic activities of APOBEC to the observed
325 restriction of viral replication, and to elucidate whether these operate mainly in virions prior to
326 infection or in the cytoplasm of infected cells [99, 100].

327 TRIM5 α proteins block retroviral infection of primate cells in a species-specific manner and
328 were originally discovered as important determinants of the resistance of monkey cells to

329HIV-1 infection [12]. The mechanisms that lead to virus inactivation by TRIM5 α proteins are
330not well understood [11]. It is thought, however, that the incoming viral capsids are rapidly
331uncoated upon entry into the cytoplasm of the host cell [101] and that the C-terminus of
332TRIM5 α interacts directly with the viral capsid and determines its antiretroviral specificity
333[101, 102]. HIV-1 is specifically blocked by TRIM5 α from Rhesus macaques and Owl
334monkeys, but only weakly restricted by human TRIM5 α [84, 85]. Therefore, the therapeutic
335targeting of TRIM5 α for treatment of HIV-1 infection may be achieved by gene therapy
336mediated delivery of rhesus or owl monkey TRIM5 α variants. Since these proteins are not
337human, a concern may be that modified cells would be eliminated by an immune response in
338treated patients. Furthermore, it remains to be elucidated whether HIV-1 can develop
339resistance against the monkey TRIM5 α variants. Recently, chimeric forms of human-rhesus
340and human-owl TRIM5 α were reported to restrict HIV-1 in transduced primary cells and in
341humanized mouse models [103, 104], thus validating chimeric forms of TRIM5 α as potential
342candidates for anti-HIV-1 gene therapy. Alternatively, it may be possible to develop
343compounds that promote the binding of TRIM5 α to HIV-1 capsids or interact directly with the
344capsids to inactivate them. Finally, it is noteworthy that other members of the TRIM family,
345such as TRIM22, may have activity against HIV-1 [105, 106]. Thus, the induction of some
346TRIM proteins may help to limit HIV-1 replication.

347The most recently identified restriction factor, tetherin (also known as BST-2, CD317, or
348HM1.24), inhibits viral spread by “tethering” fully formed mature virions on infected cell
349surfaces and preventing them from budding [14, 15]. Tetherin has broad antiviral activity: it
350inhibits a wide range of retroviruses as well as filo- and arenaviruses. Pandemic HIV-1
351strains use their Vpu protein to antagonize tetherin [14, 15, 107]. In comparison, SIVs that
352lack a *vpu* gene counteract this restriction factor by their multi-functional accessory Negative
353factor (Nef) proteins [108, 109] and HIV-2 and Ebola viruses seem to antagonize tetherin by
354their envelope glycoproteins [110-112]. The mechanisms by which these viral factors
355antagonize tetherin are not well understood but Vpu seems to sequester tetherin from the
356site of budding [14, 112], reduce its surface expression [15] and promote its beta-TrCP2-
357dependent proteasomal degradation [113, 114]. The expression of tetherin is inducible by
358interferon alpha (IFN α) and high surface levels of tetherin suppress virus release even in the
359presence of Vpu [15, 88]. Therefore, one possible therapeutic approach would be to enhance
360tetherin expression by treatment with IFN α . It has been reported that IFN α treatment in mice
361increases the levels of tetherin expression at the cell surface [115]. In early studies,
362recombinant IFN α has been used as a potential therapeutic for AIDS-associated Kaposi’s
363sarcoma caused by HHV-8 and some patients showed reduced HIV plasma viremia [116].
364Although IFN α levels are high in acute HIV-1 infection [117], evidence suggests that

365 impaired type I interferon production is observed in AIDS patients [118]. A major problem
366 with IFN- α treatment is that it has both beneficial effects - because it inhibits viral replication -
367 but also harmful consequences as it contributes to the high levels of immune activation that
368 drive progression to AIDS. Alternatively, tetherin expression and/or activity may be enhanced
369 with the use of a compound drug. Interestingly, the cholesterol-binding compound inhibitor
370 amphotericin B methyl ester (AME), previously shown to potently inhibit HIV-1 replication
371 [119], was recently shown to interfere with the anti-tetherin function of Vpu [120]. Notably,
372 recent data show that only the Vpu proteins of pandemic HIV-1 group M (major) but not of
373 non-pandemic HIV-1 group O (outlier) strains efficiently antagonize tetherin [107]. Thus,
374 efficient induction of tetherin may not only inhibit viral replication but potentially also reduce
375 the rate of sexual transmission of HIV-1.

376 Accumulating data suggest that a number of restriction factors that interfere with primate
377 lentiviral replication and are counteracted by other viral accessory genes remain to be
378 identified [10, 11]. For example, the HIV-1 Vpr and the HIV-2 Vpx proteins bind DCAF1
379 (VprBP) to engage the Cullin4 E3-ubiquitin ligase complex [121-123]. This interaction seems
380 to be required for the ability of Vpx to antagonize an as-yet-unknown host restriction in
381 human macrophages and dendritic cells [124, 125]. Thus, the major function of the majority of
382 the HIV accessory genes seems to be the antagonism of intrinsic immunity factors. However,
383 HIV-1 also evolved sophisticated mechanisms to manipulate cellular trafficking, signal
384 transduction and gene expression. In particular, the accessory viral Nef protein is well known
385 for its ability to interact with a large variety of cellular factors in order to render the infected
386 cell and their environment more conducive to viral replication and to facilitate viral immune
387 evasion [10, 11, 126, 127]. Intact *nef* genes are required for efficient HIV-1 replication in
388 infected individuals and are associated with accelerated disease progression. Thus, agents
389 disrupting the interaction of Nef with its cellular targets may have beneficial effects on the
390 clinical course of infection.

391

3924. Conclusions and future directions

393 Altogether the recent scientific advances demonstrate that the interaction between HIV-1 and
394 its human host is far more complex than previously anticipated. The identification of
395 numerous cellular factors that are exploited by HIV-1 at essentially every step of its
396 replication cycle provides a large number of potential targets for antiretroviral therapy.
397 However, a major challenge remains to separate the wheat from the chaff and important
398 questions must be addressed before the bulk of this knowledge can be translated into clinical
399 applications; e.g. which cellular factors are obligatory for HIV-1 replication in the relevant
400 primary cell types *in vivo*?; which essential interactions between viral and host factors can be

401 blocked without significant side effects?; which obligatory HIV-dependency factors can be
402 knocked-out without important physiological consequences? Moreover, the identification of a
403 potential target does not necessarily translate into the development of a therapeutic
404 molecule. The “druggability” of a candidate protein [128] depends both on its propensity to be
405 pharmacologically targeted — ideally an enzymatic domain whose endogenous binding
406 partner can be out-competed by a small drug molecule — and on its ability to be efficiently
407 delivered into target cells. While much work still remains to be done, further studies on the
408 host proteins involved in HIV replication and their inhibition or elimination are highly
409 warranted, particularly since virological and clinical analyses of the HIV-1-infected individual
410 that received the $\Delta 32/\Delta 32$ allogenic stem cell transplantation provide proof-of-concept
411 evidence that such strategies can achieve long-term control of viral replication in the absence
412 of antiretroviral therapy [39, 41].

413 It is conceivable that HIV-1 has evolved to efficiently antagonize those host defenses that are
414 most relevant for its control. As discussed above, our current knowledge suggests that
415 intrinsic host restriction factors are usually quite effective against retroviruses. Thus, it will be
416 interesting to further assess whether the efficient induction of these natural antiretroviral
417 factors may overwhelm their viral antagonists and thus allow HIV-1-infected individuals to
418 gain better control over viral replication. Finally, we should also consider that non-human
419 primates naturally infected with SIV avoid disease progression not because they are able to
420 efficiently control viral replication but because they show limited immune activation and
421 preserved mucosal immunity [129, 130]. Thus, not only strategies aiming to reduce viral
422 replication but also alternative approaches to limit the excessive harmful levels of immune
423 activation should be evaluated. Altogether, the recent scientific advances in our
424 understanding of viral pathogenesis and on the cellular factors promoting or restricting HIV
425 replication hold great promise for the development of improved treatment and prevention
426 strategies.

427

428 **ACKNOWLEDGMENTS**

429 We thank Thomas Mertens for support and Ingrid Bennett for critical reading of the
430 manuscript. This work was supported by the Deutsche Forschungsgemeinschaft (DFG). We
431 apologize to those colleagues whose studies could not be mentioned due to space
432 limitations.

433

434 **REFERENCES**

- 435 [1] E. De Clercq, The history of antiretrovirals: key discoveries over the past 25 years, Rev.
436 Med. Virol. 19 (2009) 287-299.
- 437[2] A.S. Fauci, 25 years of HIV/AIDS science: reaching the poor with research advances,
438 Cell 131 (2007) 429-432.
- 439[3] T.C. Quinn, HIV epidemiology and the effects of antiviral therapy on long-term
440 consequences, AIDS 22 (2008) S7-S12.
- 441[4] M. Mascolini, D. Richman, B. Larder, J. Mellors, C.A. Boucher, Clinical implications
442 of resistance to antiretrovirals: new resistance technologies and interpretations, Antivir.
443 Ther. 13 (2008) 319-334.
- 444[5] C. Grunfeld, Understanding the complications of antiretroviral drugs, Clin. Infect. Dis.
445 47 (2008) 575-576.
- 446[6] P. Dorr, M. Westby, S. Dobbs, P. Griffin, B. Irvine, M. Macartney, J. Mori, G. Rickett,
447 C. Smith-Burchnell, C. Napier, R. Webster, D. Armour, D. Price, B. Stammen, A.
448 Wood, M. Perros, Maraviroc (UK-427,857), a potent, orally bioavailable, and selective
449 small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human
450 immunodeficiency virus type 1 activity, Antimicrob. Agents Chemother. 49 (2005)
451 4721-4732.
- 452[7] A.L. Brass, D.M. Dykxhoorn, Y. Benita, N. Yan, A. Engelman, R.J. Xavier, J.
453 Lieberman, S.J. Elledge, Identification of host proteins required for HIV infection
454 through a functional genomic screen, Science Feb 319 (2008) 921-926.
- 455[8] R. König, Y. Zhou, D. Elleder, T.L. Diamond, G.M. Bonamy, J.T. Irelan, C.Y. Chiang,
456 B.P. Tu, P.D. De Jesus, C.E. Lilley, S. Seidel, A.M. Opaluch, J.S. Caldwell, M.D.
457 Weitzman, K.L. Kuhen, S. Bandyopadhyay, T. Ideker, A.P. Orth, L.J. Miraglia, F.D.
458 Bushman, J.A. Young, S.K. Chanda, Global analysis of host-pathogen interactions that
459 regulate early-stage HIV-1 replication, Cell 135 (2008) 49-60.
- 460[9] H. Zhou, M. Xu, Q. Huang, A.T. Gates, X.D. Zhang, J.C. Castle, E. Stec, M. Ferrer, B.
461 Strulovici, D.J. Hazuda, A.S. Espeseth, Genome-scale RNAi screen for host factors
462 required for HIV replication, Cell Host & Microbe 4 (2008) 495-504.
- 463[10] M.H. Malim, M. Emerman, HIV-1 accessory proteins--ensuring viral survival in a
464 hostile environment, Cell Host & Microbe 3 (2008) 388-398.
- 465[11] S. Neil, P. Bieniasz, Human immunodeficiency virus, restriction factors, and interferon,
466 J Interferon Cytokine Res. 29 (2009) 569-580.
- 467[12] M. Stremlau, C.M. Owens, M.J. Perron, M. Kiessling, P. Autissier, J. Sodroski, The
468 cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World
469 monkeys, Nature 427 (2004) 848-853.
- 470[13] A.M. Sheehy, N.C. Gaddis, J.D. Choi, M.H. Malim, Isolation of a human gene that
471 inhibits HIV-1 infection and is suppressed by the viral Vif protein, Nature 418 (2002)
472 646-650.
- 473[14] S.J. Neil, T. Zang, P.D. Bieniasz, Tetherin inhibits retrovirus release and is antagonized
474 by HIV-1 Vpu, Nature 451 (2008) 425-430.
- 475[15] N. Van Damme, D. Goff, C. Katsura, R.L. Jorgenson, R. Mitchell, M.C. Johnson, E.B.
476 Stephens, J. Guatelli, The interferon-induced protein BST-2 restricts HIV-1 release and
477 is downregulated from the cell surface by the viral Vpu protein, Cell Host & Microbe
478 3(2008) 245-252.
- 479[16] N. Bannert, R. Kurth, Retroelements and the human genome: new perspectives on an
480 old relation, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 14572-14579.
- 481[17] Q.J. Sattentau, R.A. Weiss, The CD4 antigen: physiological ligand and HIV receptor,
482 Cell 52 (1988) 631-633.
- 483[18] J.C. Tilton, R.W. Doms, Entry inhibitors in the treatment of HIV-1 infection, Antiviral
484 Res. (2009) in press.

- 485[19] D.R. Kuritzkes, J. Jacobson, W.G. Powderly, E. Godofsky, E. DeJesus, F. Haas, K.A.
486 Reimann, J.L. Larson, P.O. Yarbough, V. Curt, W.R. Shanahan Jr, Antiretroviral
487 activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV
488 type 1, *J. Infect. Dis.* 189 (2004) 286-291.
- 489[20] Z.Q. Zhang, M. Sorensen, M. Fung, R.T. Schooley, Synergistic in vitro antiretroviral
490 activity of a humanized monoclonal anti-CD4 antibody (TNX-355) and enfuvirtide (T-
491 20), *Antimicrob. Agents Chemother.* 50 (2006) 2231-2233.
- 492[21] G. Alkhatib, C. Combadiere, C.C. Broder, Y. Feng, P.E. Kennedy, P.M. Murphy, E.A.
493 Berger, CC-CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor
494 for macrophage-tropic HIV-1, *Science* 272 (1996) 1955-1958.
- 495[22] H. Choe, M. Farzan, Y. Sun, N. Sullivan, B. Rollins, P.D. Ponath, L. Wu, C.R. Mackay,
496 G. LaRosa, W. Newman, N. Gerard, C. Gerard, J. Sodroski, The beta-chemokine
497 receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates, *Cell* 85
498 (1996) 1135-1148.
- 499[23] H. Deng, R. Liu, W. Ellmeier, S. Choe, D. Unutmaz, M. Burkhart, P. Di Marzio, S.
500 Marmon, R.E. Sutton, C.M. Hill, C.B. Davis, S.C. Peiper, T.J. Schall, D.R. Littman,
501 N.R. Landau, Identification of a major co-receptor for primary isolates of HIV-1, *Nature*
502 381 (1996) 661-666.
- 503[24] B.J. Doranz, J. Rucker, Y. Yi, R.J. Smyth, M. Samson, S.C. Peiper, M. Parmentier, R.G.
504 Collman, R.W. Doms, A dual-tropic primary HIV-1 isolate that uses fusin and the beta-
505 chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors, *Cell* 85 (1996)
506 1149-1158.
- 507[25] E. Oberlin, A. Amara, F. Bachelier, C. Bessia, J.L. Virelizier, F. Arenzana-Seisdedos,
508 O. Schwartz, J.M. Heard, I. Clark-Lewis, D.F. Legler, M. Loetscher, M. Baggiolini, B.
509 Moser, The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents
510 infection by T-cell-line-adapted HIV-1, *Nature* 382 (1996) 833-835.
- 511[26] R. Liu, W.A. Paxton, S. Choe, D. Ceradini, S.R. Martin, R. Horuk, M.E. MacDonald, H.
512 Stuhlmann, R.A. Koup, N.R. Landau, Homozygous defect in HIV-1 coreceptor accounts
513 for resistance of some multiply-exposed individuals to HIV-1 infection, *Cell* 86 (1996)
514 367-377.
- 515[27] M. Samson, F. Libert, B.J. Doranz, J. Rucker, C. Liesnard, C.M. Farber, S. Saragosti, C.
516 Lapoumeroulie, J. Cogniaux, C. Forceille, G. Muyldermans, C. Verhofsted, G.
517 Burtonboy, M. Georges, T. Imai, S. Rana, Y. Yi, R.J. Smyth, R.G. Collman, R.W.
518 Doms, G. Vassart, M. Parmentier, Resistance to HIV-1 infection of Caucasian
519 individuals bearing mutant alleles of the CCR5 chemokine receptor gene, *Nature* 382
520 (1996) 722-725.
- 521[28] M. Dean, M. Carrington, C. Winkler, G.A. Huttley, M.W. Smith, R. Allikmets, J.J.
522 Goedert, S.P. Buchbinder, E. Vittinghoff, E. Gomperts, S. Donfield, D. Vlahov, R.
523 Kaslow, A. Saah, C. Rinaldo, R. Detels, S.J. O'Brien, Genetic restriction of HIV-1
524 infection and progression to AIDS by a deletion allele of the CKR5 structural gene
525 Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study,
526 Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study,
527 *Science* 273 (1996) 1856-1862.
- 528[29] Y. Huang, W.A. Paxton, S.M. Wolinsky, A.U. Neumann, L. Zhang, T. He, S. Kang, D.
529 Ceradini, Z. Jin, K. Yazdanbakhsh, K. Kunstman, D. Erickson, E. Dragon, N.R. Landau,
530 J. Phair, D.D. Ho, R.A. Koup, The role of a mutant CCR5 allele in HIV-1 transmission
531 and disease progression, *Nat. Med.* 2 (1996) 1240-1243.
- 532[30] G. Simmons, P.R. Clapham, L. Picard, R.E. Offord, M.M. Rosenkilde, T.W. Schwartz,
533 R. Buser, T.N. Wells, A.E. Proudfoot, Potent inhibition of HIV-1 infectivity in
534 macrophages and lymphocytes by a novel CCR5 antagonist, *Science* 276 (1997) 276-

- 535 279.
- 536[31] D.E. Mosier, G.R. Picchio, R.J. Gulizia, R. Sabbe, P. Poignard, L. Picard, R.E. Offord,
537 D.A. Thompson, J. Wilken, Highly potent RANTES analogues either prevent CCR5-
538 using human immunodeficiency virus type 1 infection in vivo or rapidly select for
539 CXCR4-using variants, *J. Virol.* 73 (1999) 3544-3550.
- 540[32] M.M. Lederman, R.S. Veazey, R. Offord, D.E. Mosier, J. Dufour, M. Mefford, M.
541 Piatak Jr, J.D. Lifson, J.R. Salkowitz, B. Rodriguez, A. Blauvelt, O. Hartley, Prevention
542 of vaginal SHIV transmission in rhesus macaques through inhibition of CCR5, *Science*
543 306 (2004) 485-487.
- 544[33] H. Gaertner, F. Cerini, J.M. Escola, G. Kuenzi, A. Melotti, R. Offord, I. Rossitto-Borlat,
545 R. Nedellec, J. Salkowitz, G. Gorochov, D. Mosier, O. Hartley, Highly potent, fully
546 recombinant anti-HIV chemokines: reengineering a low-cost microbicide, *Proc. Natl.*
547 *Acad. Sci. U. S. A.* 105 (2008) 17706-17711.
- 548[34] S. Sayana, H. Khanlou, Maraviroc: a new CCR5 antagonist, *Expert Rev. Anti Infect.*
549 *Ther.* 7 (2009) 9-19
- 550[35] J.A. Esté, A. Telenti, HIV entry inhibitors, *Lancet* 370 (2007) 81-88.
- 551[36] O.M. Klibanov, Vicriviroc, a CCR5 receptor antagonist for the potential treatment of
552 HIV infection, *Curr. Opin. Investig. Drugs* 10 (2009) 845-859.
- 553[37] J. Anderson, R. Akkina, Complete knockdown of CCR5 by lentiviral vector-expressed
554 siRNAs and protection of transgenic macrophages against HIV-1 infection, *Gene Ther.*
555 14 (2007) 1287-1297.
- 556[38] P. Kumar, H.S. Ban, S.S. Kim, H. Wu, T. Pearson, D.L. Greiner, A. Laouar, J. Yao, V.
557 Haridas, K. Habiro, Y.G. Yang, J.H. Jeong, K.Y. Lee, Y.H. Kim, S.W. Kim, M. Peipp,
558 G.H. Fey, N. Manjunath, L.D. Shultz, S.K. Lee, P. Shankar, T cell-specific siRNA
559 delivery suppresses HIV-1 infection in humanized mice, *Cell* 134 (2008) 577-586.
- 560[39] G. Hütter, D. Nowak, M. Mossner, S. Ganepola, A. Müssig, K. Allers, T. Schneider, J.
561 Hofmann, C. Kücherer, O. Blau, I.W. Blau, W.K. Hofmann, E. Thiel, Long-term control
562 of HIV by CCR5 Delta32/Delta32 stem-cell transplantation, *N. Engl. J. Med.* 360
563 (2009) 692-698.
- 564[40] M.A. Jensen, M. Coetzer, A.B. van 't Wout, L. Morris, J.I. Mullins, A reliable
565 phenotype predictor for human immunodeficiency virus type 1 subtype C based on
566 envelope V3 sequences, *J. Virol.* 80 (2006) 4698-4704.
- 567[41] G. Hütter, T. Schneider, E. Thiel, Transplantation of selected or transgenic blood stem
568 cells - a future treatment for HIV/AIDS? *J. Int. AIDS Soc.* 12 (2009) 10.
- 569[42] A. Telenti, Safety concerns about CCR5 as an antiviral target, *Curr. Opin. HIV AIDS* 4
570 (2009) 131-135.
- 571[43] C.S. Adamson, E.O. Freed, Novel approaches to inhibiting HIV-1 replication, *Antiviral*
572 *Res.* (2009) in press.
- 573[44] K. Tachibana, S. Hirota, H. Iizasa, H. Yoshida, K. Kawabata, Y. Kataoka, Y. Kitamura,
574 K. Matsushima, N. Yoshida, S. Nishikawa, T. Kishimoto, T. Nagasawa, The chemokine
575 receptor CXCR4 is essential for vascularization of the gastrointestinal tract, *Nature* 393
576 (1998) 591-594.
- 577[45] Y.R. Zou, A.H. Kottmann, M. Kuroda, I. Taniuchi, D.R. Littman, Function of the
578 chemokine receptor CXCR4 in haematopoiesis and in cerebellar development, *Nature*
579 393 (1998) 595-599.
- 580[46] D. Wong, W. Korz, Translating an Antagonist of Chemokine Receptor CXCR4: from
581 bench to bedside, *Clin. Cancer Res.* 14 (2008) 7975-7980.
- 582[47] B. Müller, H.G. Kräusslich, Antiviral strategies, *Handb. Exp. Pharmacol.* 189 (2009) 1-
583 24.
- 584[48] M. Emerman, M.H. Malim, HIV-1 regulatory/accessory genes: keys to unraveling viral

- 585 and host cell biology, *Science* 280 (1998) 1880-1884.
- 586[49] Q. Zhou, J.H. Yik, The Yin and Yang of P-TEFb regulation: implications for human
587 immunodeficiency virus gene expression and global control of cell growth and
588 differentiation, *Microbiol. Mol. Biol. Rev.* 70 (2006) 646-659.
- 589[50] P.D. Bieniasz, T.A. Grdina, H.P. Bogerd, B.R. Cullen, Recruitment of cyclin T1/P-
590 TEFb to an HIV type 1 long terminal repeat promoter proximal RNA target is both
591 necessary and sufficient for full activation of transcription, *Proc. Natl. Acad. Sci. U. S.*
592 *A.* 96 (1999) 7791-7796.
- 593[51] S.N. Richter, G. Palù, Inhibitors of HIV-1 Tat-mediated transactivation, *Curr. Med.*
594 *Chem.* 13 (2006) 1305-1315.
- 595[52] D. Harrich, N. McMillan, L. Munoz, A. Apolloni, L. Meredith, Will diverse Tat
596 interactions lead to novel antiretroviral drug targets? *Curr. Drug Targets* 7 (2006) 1595-
597 1606.
- 598[53] S.H. Chao, D.H. Price, Flavopiridol inactivates P-TEFb and blocks most RNA
599 polymerase II transcription in vivo, *J. Biol. Chem.* 276 (2001) 31793-31799.
- 600[54] V.W. Pollard, M.H. Malim, The HIV-1 Rev protein, *Annu. Rev. Microbiol.* 52 (1998)
601 491-532.
- 602[55] T.J. Hope, The ins and outs of HIV, *Rev. Arch. Biochem. Biophys.* 365 (1999) 186-91.
- 603[56] A.I. Dayton, Within you, without you: HIV-1 Rev and RNA export, *Retrovirology* 1
604 (2004) 35.
- 605[57] V.S. Yedavalli, C. Neuveut, Y.H. Chi, L. Kleiman, K.T. Jeang, Requirement of DDX3
606 DEAD box RNA helicase for HIV-1 Rev-RRE export function, *Cell* 119 (2004) 381-92.
- 607[58] M. Ishaq, J. Hu, X. Wu, Q. Fu, Y. Yang, Q. Liu, D. Guo, Knockdown of cellular RNA
608 helicase DDX3 by short hairpin RNAs suppresses HIV-1 viral replication without
609 inducing apoptosis, *Mol. Biotechnol.* 39 (2008) 231-238.
- 610[59] J.J. Rossi, C.H. June, D.B. Kohn, Genetic therapies against HIV, *Nat. Biotechnol.* 25
611 (2007) 1444-1454.
- 612[60] P. Cherepanov, G. Maertens, P. Proost, B. Devreese, J. Van Beeumen, Y. Engelborghs,
613 E. De Clercq, Z. Debyser, HIV-1 integrase forms stable tetramers and associates with
614 LEDGF/p75 protein in human cells, *J. Biol. Chem.* 278 (2003) 372-381.
- 615[61] M. Llano, D.T. Saenz, A. Meehan, P. Wongthida, M. Peretz, W.H. Walker, W. Teo,
616 E.M. Poeschla, An essential role for LEDGF/p75 in HIV integration, *Science* 314
617 (2006) 461-464.
- 618[62] S. Emiliani, A. Mousnier, K. Busschots, M. Maroun, B. Van Maele, D. Tempé, L.
619 Vandekerckhove, F. Moisant, L. Ben-Slama, M. Witvrouw, F. Christ, J.C. Rain, C.
620 Dargemont, Z. Debyser, R. Benarous, Integrase mutants defective for interaction with
621 LEDGF/p75 are impaired in chromosome tethering and HIV-1 replication, *J. Biol.*
622 *Chem.* 280 (2005) 25517-25523.
- 623[63] P. Cherepanov, Z.Y. Sun, S. Rahman, G. Maertens, G. Wagner, A. Engelman, Solution
624 structure of the HIV-1 integrase-binding domain in LEDGF/p75, *Nat. Struct. Mol. Biol.*
625 12 (2005) 526-532.
- 626[64] S. Hare, M.C. Shun, S.S. Gupta, E. Valkov, A. Engelman, P. Cherepanov, A novel co-
627 crystal structure affords the design of gain-of-function lentiviral integrase mutants in the
628 presence of modified PSIP1/LEDGF/p75, *PLoS Pathog.* 5 (2009) 259.
- 629[65] A. Engelman, P. Cherepanov, The lentiviral integrase binding protein LEDGF/p75 and
630 HIV-1 replication, *PLoS Pathog.* 4 (2008) 46.
- 631[66] U.K. von Schwedler, M. Stuchell, B. Muller, D.M. Ward, H.Y. Chung, E. Morita, H.E.
632 Wang, T. Davis, G.P. He, D.M. Cimbara, A. Scott, H.G. Kräusslich, J. Kaplan, S.G.
633 Morham, W.I. Sundquist, The Protein Network of HIV Budding, *Cell* 114 (2003) 701-
634 713.

- 635[67] J. Martin-Serrano, T. Zang, P.D. Bieniasz, Role of ESCRT-I in retroviral budding, *J. Virol.* 77 (2003) 4794–4804.
636
- 637[68] M.D. Stuchell, J.E. Garrus, B. Muller, K.M. Stray, S. Ghaffarian, R. McKinnon, H.G. Kräusslich, S.G. Morham, W.I. Sundquist, The human endosomal sorting complex required for transport (ESCRT-I) and its role in HIV-1 budding, *J. Biol. Chem.* 279 (2004) 36059–36071.
638
639
640
- 641[69] J.E. Garrus, U.K. von Schwedler, O.W. Pornillos, S.G. Morham, K.H. Zavitz, H.E. Wang, D.A. Wettstein, K.M. Stray, M. Cote, R.L. Rich, D.G. Myszka, W.I. Sundquist, Tsg101 and the vacuolar protein sorting pathway are essential for HIV-1 budding, *Cell* 107 (2001) 55-65.
642
643
644
- 645[70] J. Martin-Serrano, T. Zang, P.D. Bieniasz, HIV-1 and Ebola virus encode small peptide motifs that recruit Tsg101 to sites of particle assembly to facilitate egress, *Nat. Med.* 7 (2001) 1313-1319.
646
647
- 648[71] L. VerPlank, F. Bouamr, T.J. LaGrassa, B. Agresta, A. Kikonyogo, J. Leis, C.A. Carter, Tsg101, a homologue of ubiquitin-conjugating (E2) enzymes, binds the L domain in HIV type 1 Pr55(Gag), *Proc. Natl. Acad. Sci. U. S. A.* 98 (2001) 7724-7729.
649
650
- 651[72] A. Tavassoli, Q. Lu, J. Gam, H. Pan, S.J. Benkovic, S.N. Cohen, Inhibition of HIV budding by a genetically selected cyclic peptide targeting the Gag-TSG101 interaction, *A. C. S. Chem. Biol.* 3 (2008) 757-764.
652
653
- 654[73] B. Strack, A. Calistri, S. Craig, E. Popova, H.G. Göttlinger, AIP1/ALIX is a binding partner for HIV-1 p6 and EIAV p9 functioning in virus budding, *Cell* 114 (2003) 689-99.
655
656
- 657[74] K. Fujii, J.H. Hurley, E.O. Freed, Beyond Tsg101: the role of Alix in 'ESCRTing' HIV-1, *Nat. Rev. Microbiol.* 5 (2007) 912-916.
658
- 659[75] J. Fellay, K.V. Shianna, D. Ge, S. Colombo, B. Ledergerber, M. Weale, K. Zhang, C. Gumbs, A. Castagna, A. Cossarizza, A. Cozzi-Lepri, A. De Luca, P. Easterbrook, P. Francioli, S. Mallal, J. Martinez-Picado, J.M. Miro, N. Obel, J.P. Smith, J. Wyniger, P. Descombes, S.E. Antonarakis, N.L. Letvin, A.J. McMichael, B.F. Haynes, A. Telenti, D.B. Goldstein, A whole-genome association study of major determinants for host control of HIV-1, *Science* 317 (2007) 944-947.
660
661
662
663
664
- 665[76] W. Fu, B.E. Sanders-Bear, K.S. Katz, D.R. Maglott, K.D. Pruitt, R.G. Ptak, Human immunodeficiency virus type 1, human protein interaction database at NCBI, *Nucleic Acids Res.* 37 (2009) D417-422.
666
667
- 668[77] R.G. Ptak, W. Fu, B.E. Sanders-Bear, J.E. Dickerson, J.W. Pinney, D.L. Robertson, M.N. Rozanov, K.S. Katz, D.R. Maglott, K.D. Pruitt, C.W. Dieffenbach, Cataloguing the HIV-1 Human Protein Interaction Network, *AIDS Res. Hum. Retrovir.* 24 (2008) 1497-1502.
669
670
671
- 672[78] J.W. Pinney, J.E. Dickerson, W. Fu, B.E. Sanders-Bear, R.G. Ptak, D.L. Robertson, HIV-host interactions: a map of viral perturbation of the host system, *AIDS* 23 (2009) 549-554.
673
674
- 675[79] F.D. Bushman, N. Malani, J. Fernandes, I. D'Orso, G. Cagney, T.L. Diamond, H. Zhou, D.J. Hazuda, A.S. Espeseth, R. König, S. Bandyopadhyay, T. Ideker, S.P. Goff, N.J. Krogan, A.D. Frankel, J.A. Young, S.K. Chanda, Host cell factors in HIV replication: meta-analysis of genome-wide studies, *PLoS Pathog.* 5 (2009) 437.
676
677
678
- 679[80] D.G. Nguyen, K.C. Wolff, H. Yin, J.S. Caldwell, K.L. Kuhen, "UnPAKing" human immunodeficiency virus (HIV) replication: using small interfering RNA screening to identify novel cofactors and elucidate the role of group I PAKs in HIV infection., *J. Virol.* 80 (2006) 130-137.
680
681
682
- 683[81] M.L. Yeung, L. Houzet, V.S. Yedavalli, K.T. Jeang, A genome-wide short hairpin RNA screening of jurkat T-cells for human proteins contributing to productive HIV-1
684

- 685 replication. *J. Biol. Chem.* 284 (2009) 19463-19473.
- 686[82] S. Henriët, G. Mercenne, S. Bernacchi, J.C. Paillart, R. Marquet, Tumultuous
687 relationship between the human immunodeficiency virus type 1 viral infectivity factor
688 (Vif) and the human APOBEC-3G and APOBEC-3F restriction factors, *Microbiol. Mol.*
689 *Biol. Rev.* 73 (2009) 211-232.
- 690[83] R. Goila-Gaur, K. Strebel, HIV-1 Vif, APOBEC, and intrinsic immunity, *Retrovirology*
691 5 (2008) 51.
- 692[84] S. Nisole, J.P. Stoye, A. Saïb, TRIM family proteins: retroviral restriction and antiviral
693 defence, *Nat. Rev. Microbiol.* 3 (2005) 799-808.
- 694[85] G.J. Towers GJ, The control of viral infection by tripartite motif proteins and
695 cyclophilin A, *Retrovirology* 4 (2007) 40.
- 696[86] S.L. Sawyer, M. Emerman, H.S. Malik, Ancient adaptive evolution of the primate
697 antiviral DNA-editing enzyme APOBEC3G, *PLoS Biol.* 2 (2004) 275.
- 698[87] S.L. Sawyer, L.I. Wu, M. Emerman, H.S. Malik, Positive selection of primate
699 TRIM5 α identifies a critical species-specific retroviral restriction domain, *Proc.*
700 *Natl. Acad. Sci. U. S. A.* 102 (2005) 2832-2837.
- 701[88] N.W. McNatt, T. Zang, T. Hatzioannou, M. Bartlett, I.B. Fofana, W.E. Johnsonm, S.J.
702 Neil, P.D. Bieniasz, Species-specific activity of HIV-1 Vpu and positive selection of
703 tetherin transmembrane domain variants *PLoS Pathog.* 5 (2009) 300.
- 704[89] B. Song, B. Gold, C. O'Huigin, H. Javanbakht, X. Li, M. Stremlau, C. Winkler, M.
705 Dean, J. Sodroski, The B302(SPRY) domain of the retroviral restriction factor
706 TRIM5 α exhibits lineage-specific length and sequence variation in primates, *J.*
707 *Viol.* 79 (2005) 6111-6121.
- 708[90] C. Esnault, O. Heidmann, F. Delebecque, M. Dewannieux, D. Ribet, A.J. Hance, T.
709 Heidmann, O. Schwartz, APOBEC3G cytidine deaminase inhibits retrotransposition of
710 endogenous retroviruses, *Nature* 433 (2005) 430-433.
- 711[91] Y.L. Chiu, W.C. Greene, The APOBEC3 cytidine deaminases: an innate defensive
712 network opposing exogenous retroviruses and endogenous retroelements, *Annu. Rev.*
713 *Immunol.* 26 (2008) 317-353.
- 714[92] A.M. Land, T.B. Ball, M. Luo, R. Pilon, P. Sandstrom, J.E. Embree, C. Wachihi, J.
715 Kimani, F.A. Plummer, Human immunodeficiency virus (HIV) type 1 proviral
716 hypermutation correlates with CD4 count in HIV-infected women from Kenya, *J. Virol.*
717 82 (2008) 8172-8182.
- 718[93] A. Piantadosi, D. Humes, B. Chohan, R.S. McClelland, J. Overbaugh, Analysis of the
719 percentage of human immunodeficiency virus type 1 sequences that are hypermutated
720 and markers of disease progression in a longitudinal cohort, including one individual
721 with a partially defective Vif, *J. Virol.* 83 (2009) 7805-7814.
- 722[94] N.K. Ulenga, A.D. Sarr, D. Hamel, J.L. Sankale, S. Mboup, P.J. Kanki, The level of
723 APOBEC3G (hA3G)-related G-to-A mutations does not correlate with viral load in HIV
724 type 1-infected individuals, *AIDS Res. Hum. Retrovir.* 24 (2008) 1285-1290.
- 725[95] R. Nathans, H. Cao, N. Sharova, A. Ali, M. Sharkey, R. Stranska, M. Stevenson, T.M.
726 Rana, Small-molecule inhibition of HIV-1 Vif, *Nat. Biotechnol.* 26 (2008) 1187-1192.
- 727[96] R.S. Harris, Enhancing immunity to HIV through APOBEC, *Nat. Biotechnol.* 26 (2008)
728 1089-1090.
- 729[97] K. Chen, J. Huang, C. Zhang, S. Huang, G. Nunnari, F.X. Wang, X. Tong, L. Gao, K.
730 Nikisher, H. Zhang, Alpha interferon potently enhances the anti-human
731 immunodeficiency virus type 1 activity of APOBEC3G in resting primary CD4 T cells,
732 *J. Virol.* 80 (2006) 7645-7657.
- 733[98] G. Peng, K.J. Lei, W. Jin, T. Greenwell-Wild, S.M. Wahl: Induction of APOBEC3
734 family proteins, a defensive maneuver underlying interferon-induced anti-HIV-1

- 735 activity, *J. Exp. Med.* 203 (2006) 41-46.
- 736[99] S. Henriët, G. Mercenne, S. Bernacchi, J.C. Paillart, R. Marquet, Tumultuous
737 relationship between the human immunodeficiency virus type 1 viral infectivity factor
738 (Vif) and the human APOBEC-3G and APOBEC-3F restriction factors, *Microbiol. Mol.*
739 *Biol. Rev.* 73 (2009) 211-232.
- 740[100] R. Goila-Gaur, K. Strebel, HIV-1 Vif, APOBEC, and intrinsic immunity, *Retrovirology*
741 5 (2008) 51.
- 742[101] M. Stremlau, M. Perron, M. Lee, Y. Li, B. Song, H. Javanbakht, F. Diaz-Griffero, D.J.
743 Anderson, W.I. Sundquist, J. Sodroski, Specific recognition and accelerated uncoating
744 of retroviral capsids by the TRIM5 α restriction factor, *Proc. Natl. Acad. Sci. U. S.*
745 *A.* 103 (2006) 5514-5519.
- 746[102] S. Sebastian, J. Luban, TRIM5 α selectively binds a restriction-sensitive retroviral
747 capsid, *Retrovirology* 2 (2005) 40.
- 748[103] J. Anderson, R. Akkina, Human immunodeficiency virus type 1 restriction by human-
749 rhesus chimeric tripartite motif 5 α (TRIM 5 α) in CD34(+) cell-derived
750 macrophages in vitro and in T cells in vivo in severe combined immunodeficient (SCID-
751 hu) mice transplanted with human fetal tissue, *Hum. Gene Ther.* 2008 Mar;19(3):217-
752 228.
- 753[104] M.R. Neagu, P. Ziegler, T. Pertel, C. Strambio-De-Castillia, C. Grütter, G. Martinetti,
754 L. Mazzucchelli, M. Grütter, M.G. Manz, J. Luban, Potent inhibition of HIV-1 by
755 TRIM5-cyclophilin fusion proteins engineered from human components, *J. Clin. Invest.*
756 119 (2009) 3035-3047.
- 757[105] L. Carthagen, A. Bergamaschi, J.M. Luna, A. David, P.D. Uchil, F. Margottin-Goguet,
758 W. Mothes, U. Hazan, C. Transy, G. Pancino, S. Nisole, Human TRIM gene expression
759 in response to interferons, *PLoS One* 4 (2009) 4894.
- 760[106] P.D. Uchil, B.P. Quinlan, W.T. Chan, J.M. Luna, W. Mothes, TRIM E3 ligases
761 interfere with early and late stages of the retroviral life cycle, *PLoS Pathog.* 4 (2008) 16.
- 762[107] D. Sauter, M. Schindler, A. Specht, W.N. Landford, J. Münch, K.A. Kim, J. Votteler,
763 U. Schubert, F. Bibollet-Ruche, B.F. Keele, J. Takehisa, Y. Ogando, C. Ochsenbauer,
764 J.C. Kappes, A. Ajouba, M. Peeters, G.H. Learn, G. Shaw, P.M. Sharp, P. Bieniasz,
765 B.H. Hahn, T. Hatziioannou, F. Kirchhoff, The evolution of pandemic and non-
766 pandemic HIV-1 strains has been driven by Tetherin antagonism, *Cell Host & Microbe*
767 (2009) in press.
- 768[108] B. Jia, R. Serra-Moreno, W. Neidermyer, A. Rahmberg, J. Mackey, I.B. Fofana, W.E.
769 Johnson, S. Westmoreland, D.T. Evans, Species-specific activity of SIV Nef and HIV-1
770 Vpu in overcoming restriction by tetherin/BST2, *PLoS Pathog.* 5 (2009) 429.
- 771[109] F. Zhang, S.J. Wilson, W.C. Landford, B. Virgen, D. Gregory, M.C. Johnson, J. Munch,
772 F. Kirchhoff, P.D. Bieniasz, T. Hatziioannou, Nef proteins from simian
773 immunodeficiency viruses are tetherin antagonists, *Cell Host & Microbe* 6 (2009) 54-
774 67.
- 775[110] A. Le Tortorec A, S.J. Neil, Antagonism and intracellular sequestration of human
776 tetherin by the HIV-2 envelope glycoprotein, *J. Virol.* (2009) in press.
- 777[111] R.L. Kaletsky, J.R. Francica, C. Agrawal-Gamse, P. Bates, Tetherin-mediated
778 restriction of filovirus budding is antagonized by the Ebola glycoprotein, *Proc. Natl.*
779 *Acad. Sci. U. S. A.* 106 (2009) 2886-2891.
- 780[112] N. Jouvenet, S.J. Neil, M. Zhadina, T. Zang, Z. Kratovac, Y. Lee, M. McNatt, T.
781 Hatziioannou, P.D. Bieniasz, Broad-spectrum inhibition of retroviral and filoviral
782 particle release by tetherin, *J. Virol.* 83 (2009) 1837-1844.
- 783[113] C. Goffinet, I. Allespach, S. Homann, H.M. Tervo, A. Habermann, D. Rupp, L.
784 Oberbremer, C. Kern, N. Tibroni, S. Welsch, J. Krijnse-Locker, G. Banting, H.G.

- 785 Kräusslich, O.T. Fackler, O.T. Keppler, HIV-1 antagonism of CD317 is species specific
 786 and involves Vpu-mediated proteasomal degradation of the restriction factor, *Cell Host*
 787 & *Microbe* 5 (2009) 285-297.
- 788[114] B. Mangeat, G. Gers-Huber, M. Lehmann, M. Zufferey, J. Luban, V. Piguet, HIV-1
 789 Vpu neutralizes the antiviral factor Tetherin/BST-2 by binding it and directing its beta-
 790 TrCP2-dependent degradation, *PLoS Pathog.* 5 (2009) 574.
- 791[115] S. Kawai, Y. Azuma, E. Fujii, K. Furugaki, S. Ozaki, T. Matsumoto, M. Kosaka, H.
 792 Yamada-Okabe, Interferon-alpha enhances CD317 expression and the antitumor activity
 793 of anti-CD317 monoclonal antibody in renal cell carcinoma xenograft models, *Cancer*
 794 *Sci.* 99 (2008) 2461-2466.
- 795[116] H.C. Lane, J.A. Kovacs, J. Feinberg, B. Herpin, V. Davey, R. Walker, L. Deyton, J.A.
 796 Metcalf, M. Baseler, N. Salzman, Anti-retroviral effects of interferon-alpha in AIDS-
 797 associated Kaposi's sarcoma, *Lancet* 2 (1988) 1218-1222.
- 798[117] A.R. Stacey, P.J. Norris, L. Qin, E.A. Haygreen, E. Taylor, J. Heitman, M. Lebedeva,
 799 A. DeCamp, D. Li, D. Grove, S.G. Self, P. Borrow, Induction of a striking systemic
 800 cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1
 801 infection, in contrast to more modest and delayed responses in acute hepatitis B and C
 802 virus infections, *J. Virol.* 83 (2009) 3719-3733.
- 803[118] A. Hosmalin, P. Lebon, Type I IFN interferon production in HIV-infected patients, *J.*
 804 *Leukoc. Biol.* 80 (200) 984-993.
- 805[119] A.A. Waheed, S.D. Ablan, M.K. Mankowski, J.E. Cummins, R.G. Ptak, C.P. Schaffner,
 806 E.O. Freed, Inhibition of HIV-1 replication by amphotericin B methyl ester: selection
 807 for resistant variants, *J. Biol. Chem.* 281 (2006) 28699-28711.
- 808[120] A.A. Waheed, S.D. Ablan, F. Soheilian, K. Nagashima, A. Ono, C.P. Schaffner, E.O.
 809 Freed, Inhibition of human immunodeficiency virus type 1 assembly and release by the
 810 cholesterol-binding compound amphotericin B methyl ester: evidence for Vpu
 811 dependence, *J. Virol.* 82 (2008) 9776-9781.
- 812[121] K. Hrecka, M. Gierszewska, S. Srivastava, L. Kozaczekiewicz, S.K. Swanson, L.
 813 Florens, M.P. Washburn, J. Skowronski, Lentiviral Vpr usurps Cul4-DDB1[VprBP] E3
 814 ubiquitin ligase to modulate cell cycle, *Proc. Natl. Acad. Sci. U. S. A.* 104 (2007)
 815 11778-11783.
- 816[122] E. Le Rouzic, N. Belaïdouni, E. Estrabaud, M. Morel, J.C. Rain, C. Transy, F.
 817 Margottin-Goguet, HIV1 Vpr arrests the cell cycle by recruiting DCAF1/VprBP, a
 818 receptor of the Cul4-DDB1 ubiquitin ligase, *Cell Cycle* 6 (2007) 182-188.
- 819[123] B. Schröfelbauer, Y. Hakata, N.R. Landau, HIV-1 Vpr function is mediated by
 820 interaction with the damage-specific DNA-binding protein DDB1, *Proc. Natl. Acad.*
 821 *Sci. U. S. A.* 104 (2007) 4130-4135.
- 822[124] C. Goujon, L. Rivière, L. Jarrosson-Wuilleme, J. Bernaud, D. Rigal, J.L. Darlix, A.
 823 Cimarelli, SIVSM/HIV-2 Vpx proteins promote retroviral escape from a proteasome-
 824 dependent restriction pathway present in human dendritic cells, *Retrovirology* 4 (2007)
 825 2.
- 826[125] N. Sharova, Y. Wu, X. Zhu, R. Stranska, R. Kaushik, M. Sharkey, M. Stevenson,
 827 Primate lentiviral Vpx commandeers DDB1 to counteract a macrophage restriction,
 828 *PLoS Pathog.* 4 (2008) 57.
- 829[126] F. Kirchhoff, M. Schindler, A. Specht, N. Arhel, J. Münch, Role of Nef in primate
 830 lentiviral immunopathogenesis, *Cell. Mol. Life Sci.* 65 (2008) 2621-3636.
- 831[127] N. Arhel, F. Kirchhoff, Implications of Nef: Host cell interactions in viral persistence
 832 and progression to AIDS, *Curr. Top. Microbiol. Immunol.* (2009) in press.
- 833[128] A.L. Hopkins, C.R. Groom, The druggable genome, *Nat. Rev. Drug Discov.* 1 (2002)
 834 727-730.

835[129] D.L. Sodora, J.S. Allan, C. Apetrei, J.M. Brenchley, D.C. Douek, J.G. Else, J.D. Estes,
836 B.H. Hahn, V.M. Hirsch, A. Kaur, F. Kirchhoff, M. Muller-Trutwin, I. Pandrea, J.E.
837 Schmitz, G. Silvestri, Toward an AIDS vaccine: lessons from natural simian
838 immunodeficiency virus infections of African nonhuman primate hosts, *Nat. Med.* 15
839 (2009) 861-865.

840[130] M. Paiardini, I. Pandrea, C. Apetrei, G. Silvestri, Lessons learned from the natural hosts
841 of HIV-related viruses, *Annu. Rev. Med.* 60 (2009) 485-495.

842

843

844

845

846 **FIGURE LEGENDS**

847 **Fig. 1.** Viral replication cycle and the steps currently inhibited by HAART. Viral proteins
848 involved in the individual steps are indicated in black and antiretroviral agents blocking them
849 in blue.

850 **Fig. 2.** Intrinsic host restriction factors and their viral antagonists. As schematically indicated,
851 TRIM5 α interacts with the incoming HIV-1 capsids and may induce accelerated uncoating by
852 proteasomal degradation. The accessory viral Vif protein binds to a Cullin5-based ubiquitin
853 ligase complex and to APOBEC3G (3G) to induce the degradation of the latter in
854 proteasomes. In the absence of Vif, APOBEC3G is incorporated into the budding virions and
855 causes lethal G to A hypermutations of the retroviral genome in the next round of infection.
856 Tetherin prevents the release of nascent mature viral particles from the cell surface and is
857 antagonized by Vpu. The exact mechanism by which Vpu counteracts tetherin remains to be
858 identified but may involve direct interaction and beta-TrCP2-dependent degradation of
859 tetherin leading to its sequestration from budding virions.

860 Table 1: Selected host factors involved in HIV-1 infection.

861

CATEGORY	EXAMPLE
Surface molecules	Clusters of differentiation; Integrins; Chemokines; MHC; Lectins; Syndecans; Inositol triphosphate receptor
Endocytosis	Caveolin; Clathrin; COPI system of vesicular transport
Intracellular receptors	Steroid receptors; Nuclear receptors
Signaling	Ras family; Tyrosine and serine/threonine kinases; Phosphatases; cAMP Phosphodiesterases
Cytoskeleton	Actin, microtubule, and intermediate filament components and associated proteins
Proteasomal degradation	Proteasome subunits; Ubiquitin-conjugating enzymes, -ligases and other associated proteins
Lysosomal degradation	Breakdown enzymes; vacuolar ATPases
Nuclear import	Nucleoporins; Karyopherins; Ran binding proteins
Chromatin	Histones; Histone clusters; Histone deacetylases; Chromatin modifying proteins; Regulators of DNA repair/telomere length
Transcription & DNA binding	Transcription factors; Co-activators; Transcription elongation factors; RNA polymerases; Mediator complex; DNA binding proteins
Nuclear export	RNA export factors; Nuclear Export Signal dependent transport
RNA splicing	Splicing factors
Translation & RNA binding	Translation initiation factors; Translation elongation factors; RNA helicases; Ribonuclear proteins; Ribosome-associated; Protein ER translocation
Protein assembly/ Protein-protein interactions	Tripartite motif proteins; Ankyrin repeat domains; Heat shock proteins; chaperones
Protein modifications	Acetyltransferases; Myristoyltransferases; Peptidases; Proteases
Metabolism	Isomerases; Glycosyltransferases; Convertases; Phospholipases and other metabolic enzymes
Apoptosis	Inducers of apoptosis
Cell cycle & proliferation	Cyclins, Cyclin-dependent kinases; Cell division control proteins
Multivesicular body formation	ESCRT machinery; synaptic proteins
Cytokines & secreted proteins	Interleukins; Tumor necrosis factor
Others	Antioxidants/metal binding; Ion channels; Complement

862

863

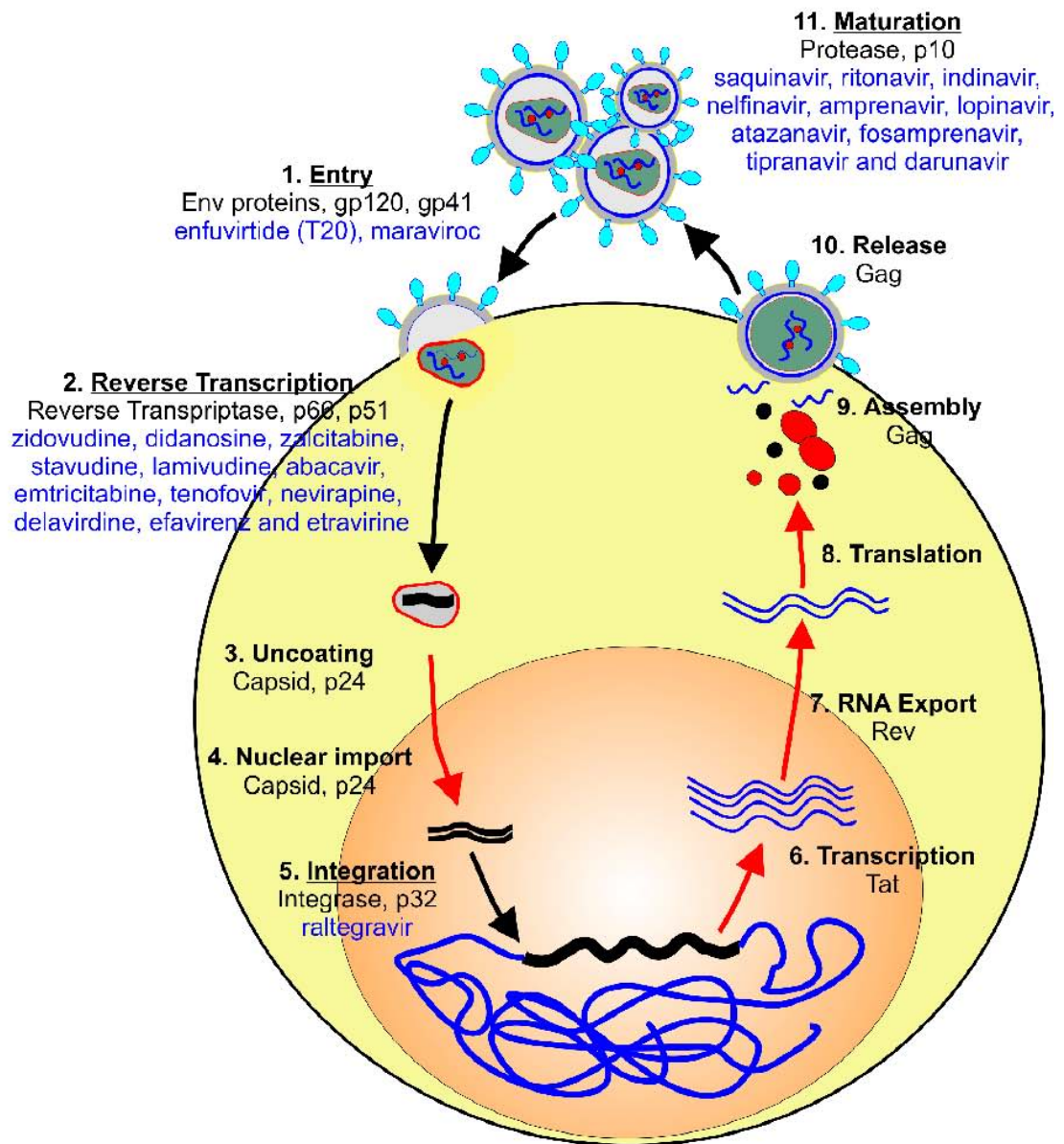
864 Shown are examples of host factors identified more than once in databases of host proteins whose
865 knock-down attenuates HIV-1 infection, of single-nucleotide polymorphisms (SNPs) proposed to be
866 associated with disease progression, and of host proteins reported to interact with one or more viral
867 component [7, 8, 9, 75-79]. The list is not complete and the relevance of most of these cellular factors
868 in primary HIV-1-infected cells remains to be confirmed.

869

870

871

Arhel & Kirchhoff, Fig.1



Arhel & Kirchhoff, Fig. 2

